

REMARKS

Claims 9-20 are pending and have been rejected. Claims 9-20 remain in the case.

Claims 11 and 12 are objected to as being of improper dependent form. Claims 11 and 12 have been amended to be of proper dependent form.

Claims 9-12 and 16-20 are rejected under the first paragraph of Section 112. The examiner alleges that the specification only is enabling for a method for detecting a tissue in a patient by administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to one of the specific F-18 labeled peptides that are recited in claims 13-15, or a low molecular weight hapten conjugated to one of these F-18 labeled peptides, and then administering one of the specific F-18 labeled peptides recited in claims 13-15 or the hapten conjugate thereof, and detecting that F-18 labeled peptide by positron emission tomography. The examiner finds that bispecific antibodies and antibody fragments in which the other arm is specific to “*any* F-18 labeled peptide or and low molecular weight hapten conjugated to *any* F-18 labeled peptide” are not enabled.

The basis for the allegation of lack of enablement is that, other than the specific F-18 labeled peptides recited in claims 13-15, there is insufficient guidance about the structure (amino acid residues) of any of the F-18 labeled peptides. The examiner elaborates that “without the specific amino acid residues, one of skill in the art cannot even contemplate of making such antibody that would have one arm specific for any F-18 labeled peptide and one arm would be specific for any tissue in a patient,” and cites Kuby *et al.* as showing that “immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.”

Yet the making of antibodies to *any* immunogen is a straightforward and routine matter. More particularly, antibodies to peptide backbones are generated by well-known methods for antibody production. For example, injection of an immunogen, such as (peptide)_n-KLH, wherein KLH is keyhole limpet hemocyanin, and n=1-30, in complete Freund's adjuvant, followed by two subsequent injections of the same immunogen suspended in incomplete Freund's adjuvant into immunocompetent animals, is followed three days after an i.v. boost of antigen, by spleen cell harvesting. Harvested spleen cells are then fused with Sp2/0-Ag14 myeloma cells and culture supernatants of the resulting clones analyzed for

anti-peptide reactivity using a direct-binding ELISA. Fine specificity of generated antibodies can be analyzed for by using peptide fragments of the original immunogen. These fragments can be prepared readily using an automated peptide synthesizer. For antibody production, enzyme-deficient hybridomas are isolated to enable selection of fused cell lines. This technique also can be used to raise antibodies to one or more of the low molecular weight haptens, chelates comprising the linker, e.g., In(III)-DTPA chelates. Monoclonal mouse antibodies to an In(III)-di-DTPA are known (Barbet *et al.*, U.S. Pat. Nos. 5,256,395).

After the initial raising of antibodies to the immunogen, the antibodies can be sequenced and subsequently prepared by recombinant techniques. Humanization and chimerization of murine antibodies and antibody fragments are well known to those skilled in the art. For example, humanized monoclonal antibodies are produced by transferring mouse complementary determining regions from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, and then, substituting human residues in the framework regions of the murine counterparts. The use of antibody components derived from humanized monoclonal antibodies obviates potential problems associated with the immunogenicity of murine constant regions. General techniques for cloning murine immunoglobulin variable domains are described, for example, by the publication of Orlandi *et al.*, *Proc. Nat'l Acad. Sci. USA* 86: 3833 (1989). Techniques for producing humanized Mabs are described, for example, by Jones *et al.*, *Nature* 321: 522 (1986), Riechmann *et al.*, *Nature* 332: 323 (1988), Verhoeyen *et al.*, *Science* 239: 1534 (1988), Carter *et al.*, *Proc. Nat'l Acad. Sci. USA* 89: 4285 (1992), Sandhu, *Crit. Rev. Biotech.* 12: 437 (1992), and Singer *et al.*, *J. Immun.* 150: 2844 (1993).

Alternatively, fully human antibodies can be obtained from transgenic non-human animals. See, e.g., Mendez *et al.*, *Nature Genetics*, 15: 146-156 (1997); U.S. Pat. No. 5,633,425. For example, human antibodies can be recovered from transgenic mice possessing human immunoglobulin loci. The mouse humoral immune system is humanized by inactivating the endogenous immunoglobulin genes and introducing human immunoglobulin loci. The human immunoglobulin loci are exceedingly complex and comprise a large number of discrete segments which together occupy almost 0.2% of the human genome. To ensure that transgenic mice are capable of producing adequate repertoires of antibodies, large portions of human heavy- and light-chain loci must be introduced into the mouse genome. This is accomplished in a stepwise process beginning with the formation of yeast artificial chromosomes (YACs) containing either human heavy- or light-chain immunoglobulin loci in germline configuration. All of the foregoing description can be found in U.S. Serial no. 09/823,746, the regular filing of

provisional application no. 60/090,142, which is mentioned on page 4 of the application and incorporated by reference.

Thus, a skilled artisan readily can generate antibodies to any immunogen, and from those antibodies can prepare antibody fragments that are specific to the immunogen. These antibodies and fragments may be monoclonal, as in claim 18, or humanized, as in claim 19. The fact that different peptide sequences produce antibodies that have different specificities does not lead to a lack of enablement of the present claims, since a skilled artisan could generate an antibody for any peptide, without even knowing the amino acid sequence of the peptide! As noted by the examiner, in addition to having different specificities, antibodies to different peptides also may have different affinities. However, the determination of affinities, and the selection of those antibodies with the best affinities, also are routine and within the level of skill in this art.

Claims 9-12 and 16-20 also are rejected under the first paragraph of Section 112 as containing subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 9-12 and 16-20 are original claims. As to original claims, possession may be shown in many ways. For example, possession may be shown, *inter alia*, by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.¹

For each claim drawn to a genus, as in claim 9, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice. A representative number of species means that the species which are adequately described are representative of the entire genus. There may be situations where one species adequately supports a genus. Furthermore, what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes

¹ USPTO Written Description Guidelines.

or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.²

In the present case, the exemplified species demonstrate possession of the genus of "F-18 labeled peptides" that is recited in claim 9. The level of skill in this art is very high, and based on this, and the teaching found in the present disclosure, a skilled artisan can label any thiol-containing peptide. The technique entails reacting the thiol group with an F-18 bound labeling reagent which has a group that is reactive with thiols. Even peptides that do not originally comprise a free thiol group can be labeled in accordance with the present invention by first modifying the peptide to add a free thiol group by methods known to those skilled in the art. For example, the peptide can be thiolated with reagents such as 2-iminothiolane, or intrinsic disulfide bonds such as cysteine residues can be reduced. A combination of both modifications also can be performed, such as acylation of lysine residues with N-succinimidyl-3-(2-pyridylthio)-propionate (SPDP) followed by the controlled reduction of the appended disulfide bond. These techniques are discussed at the top of page 6.

Based on the foregoing, it is believed that all claims are in condition for allowance. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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² USPTO Written Description Guidelines.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

11. (Amended) The method according to claim 10, wherein the F-18-labeled peptide is labeled by [the method according to claim 1] a method comprising reacting a peptide comprising a free thiol group with a labelling reagent having the general formula $^{18}\text{F}-(\text{CH}_2)_m-\text{CR}_1\text{R}_2-(\text{CH}_2)_n-\text{X}$, wherein:

n is 0, 1 or 2;

m is 0, 1 or 2;

and n+m is 0, 1, or 2;

X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups, and 3-sulfo-maleimide; and

R₁ and R₂ are the same or different and are selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, hydrogen, -CONH₂, carboxyl, hydroxyl, sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'₂, or COR', wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH₂, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is a C₁-C₆ alkyl or phenyl.

12. (Amended) The method according to claim 10, wherein the F-18-labeled peptide is labeled by [the method according to claim 6] a method comprising reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate.